Remarks:

In the Office Action dated May 29, 2008, claims 21-35 and 37-43 in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 22-35 and 37-43 remain in this application and claims 1-21 and 36 have been canceled.

Claims 21-35 and 37-41 were rejected under 35 USC §112, first paragraph as failing to comply with the written description requirement. Claim 21 has been canceled and the dependent claims amended to depend from claim 42 which was not included in this rejection. In addition, claims 40 and 41 have been amended to indicate that when the coating is a gastric juice resistant coating selected from the group consisting of anionic copolymer of methacrylic acid and methyl methacrylate USP/NF, cellulose acetate phthalate, cellulose acetate trimellitate methylhydroxypropylcellulose phthalate, and polyvinyl acetate phthalate, which does not dissolve during contact with the digestive solution in a patient's stomach, a pore forming agent is included with the coating to separate the coating from the core during contact with digestive solution in the patient's stomach as in claim 42. Since these limitations are in unamended claim 42, these amendments do not raise any new issues. In view of these amendments, applicants request that this rejection be withdrawn.

Claim 43 was rejected as including new matter regarding a coating containing methylhydroxypropylcellulose phthalate and lactose. Claim 43 has been amended to recite methylhydroxypropylcellulose and lactose. Example 3 in

the present application discloses such a coating. In view of the above amendments, applicants request that this rejection be withdrawn.

Claims 21-35 and 37-43 were rejected under 35 USC §112, first paragraph, as failing to comply with the enablement requirement regarding the release of 30% of the ibandronate into the stomach. The office action contends that all of the coatings recited in claim 42 are enteric and thus would not be expected to release the drug in the stomach. Applicants respectfully point out that this statement is erroneous. While enteric coatings release the drug in the intestine, the coatings recited in the claims are not enteric as some of the coatings dissolve in the stomach and the coatings which use gastric juice resistant films, include pore formers which cause the gastric juice resistant film to break apart and be released in the patient's stomach. Applicants point out that a coating comprising a cationic polymer with dimethylaminoethyl methacrylate as a functional group (e.g. Eudragit® E) dissolves in the acid medium of the stomach. Eudragit® E is considered to be an immediate release coating not an enteric coating. A copy of the manufacturer's product description as shown at http://www.pharma-polymere.de/pharmapolymers/en/eudragit/protectivecoatings/ is enclosed. Coatings containing a copolymer selected from the group consisting of ammonio methacrylate copolymer Type A and Type B USP/NF (e.g. Eudragit® RL and Eudragit® RS) or a copolymer of ethyl acrylate and methyl methacrylate with neutral character (Eudragit® NE 30 D) are not considered to be enteric coatings either but are sustained release formulations as shown by

http://www.pharma-polymere.de/pharmapolymers/en/eudragit/sustainedreleaseformulations/ (copy enclosed). Though coatings containing anionic copolymer of methacrylic acid and methyl methacrylate, cellulose acetate phthalate, cellulose acetate trimellitate, methylhydroxypropylcellulose phthalate and polyvinyl acetate phthalate are usually gastric juice resistant, the present claims indicate that pore forming agents are used when the coating is a gastric juice resistant coating selected from the group consisting of anionic copolymer of methacrylic acid and methyl methacrylate USP/NF, cellulose acetate phthalate, cellulose acetate trimellitate methylhydroxypropylcellulose phthalate, and polyvinyl acetate phthalate, which does not dissolve during contact with the digestive solution in a patient's stomach. Pore forming agents are known in the art as shown by U.S. Patent Nos. 4,200098; 4,285,987; 4,743,248, 4,931,285, 7,060734, and 7,087,243 as well as other issued patents. The office action states that no evidence has been provided that combinations of enteric polymers and pore formers were well known in the art at the time of the invention. U.S. Patent Nos. 5,639,476; 6,024982; and 4,629,619 show that the combination of sustained release and enteric coatings with pore formers was known in the art before the present invention was made. U.S. Patent No. 5,639,476 discusses a coating containing a copolymer selected from the group consisting of ammonio methacrylate copolymer Type A and Type B USP/NF, (e.g. Eudragit® RL and Eudragit® RS) at column 9, lines 19-54; an anionic copolymer of methacrylic acid and methyl methacrylate (e.g. Eudragit® L and Eudragit® S) at column 10, lines

6-27; and pore formers at column 10, line 36 to column 11, line 46. U.S. Patent No. 5,639,476 states at column 10, lines 36-44 that:

> "The release of the active agent from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more pore-formers which can be inorganic or organic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. Upon exposure to fluids in the environment of use, the pore-formers are, e.g., dissolved, and channels and pores are formed that fill with the environmental fluid."

U.S. Patent No. 5,639,476 indicates at column 12, lines 1-24, that formulations have been made which release 0-42.5% of the active agent after 1 hour, 5-60% after 2 hours, 15-75% after 4 hours and 20-90% after 8 hours. Another formulation disclosed in U.S. Patent No. 5,639,476 released 0-42.5% of the active agent after 1 hour, 25-55% after 2 hours, 45-75% after 4 hours and >55% after 6 hours. In view of the knowledge in the prior art, one skilled in the art would know that the coatings and pore forming agents could be adjusted to result in the desired dissolution rate.

As previously indicated, the present invention lies in the discovery that bone disease can be treated with ibandronate which is in an oral formulation and which is released in a patient's stomach to avoid irritations to the upper gastrointestinal tract but is still rapidly resorbed in sufficient amounts. The prior art uncoated formulations caused upper gastrointestinal irritations and the prior art coated formulations had reduced and/or variable resorption. The present inventors have found that both of these disadvantages can be avoided by using a coating which dissolves or is released from the core (e.g. by using pore forming

agents) upon contact with the digestive solution in the patient's stomach. Contrary to statements made in the office action, the coatings recited in the present claims are not all enteric coatings and the claims indicate that the coatings which are enteric coatings include pore forming agents which separate the coating from the core in the patient's stomach. In view of the fact that the coatings and the pore forming agents recited in the present claims have been used together with other active agents in the prior art and are well known in the art, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 22-35 and 37-43 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By 

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EUDRAGIT
Quick Starts
Enteric Coatings
Sustained-release Formulations
Protective Coatings
Melt Extrusion
Regulatory & Toxicology
Packaging & Delivery

Protective Coatings

Many active ingredients require a protective coating to increase their stability and improve t
EUDRAGIT® coatings dissolve in the acid medium of the stomach to rapidly release the act
increase patient compliance by masking tastes and odors. Even thin layers of EUDRAGIT®
economical application. Pharma Polymers offer various cationic EUDRAGIT® E grades for

Applications	EUDRAGIT® Grades	Availability	Functionality
Taste masking, odor masking	EUDRAGIT® E 100	Granules	Cationic polymer with dimethylaminoethyl methacrylat functional group
Insulating coatings	EUDRAGIT® E PO	Powder	

Application benefits of protective EUDRAGIT® coatings:

- PH-dependent drug release
- Protection of sensitive actives
- Taste and odor masking
- Moisture protection
- Good storage stability
- Improved passage of the dosage form
- Smooth and glossy surfaces, good colorcoating

EUDRAGIT
Quick Starts
Enteric Coatings
Sustained-release Formulations
Protective Coatings
Melt Extrusion
Regulatory & Toxicology
Packaging & Delivery

Enteric Coatings

Many pharmaceutical dosage forms irritate the stomach due to their chemical properties. Ot and through the action of enzymes, thus becoming less effective.

The EUDRAGIT® grades for enteric coatings are based on anionic polymers of methacrylic a functional group. They dissolve at ranges from pH 5.5 to pH 7. The different products are organic solvents (see product overview)

Applications	EUDRAGIT® Grades	Availability	Functionality
Drug delivery in duodenum	EUDRAGIT® L 100-55	Powder	Anionic polymers with methacrylic acid as a funct group
	EUDRAGIT® L 30 D-55	Aqueous dispersion 30%	
Drug delivery in jejunum	EUDRAGIT® L 100	Powder	
Drug delivery in ileum	EUDRAGIT® S 100	Powder	
Colon delivery	EUDRAGIT® FS 30 D	Aqueous dispersion 30%	

Application benefits of enteric EUDRAGIT® coatings:

- PH-dependent drug release
- Protection of actives sensitive to gastric fluid
- Protection of gastric mucosa from aggressive actives
- Increase in drug effectiveness
- Good storage stability
- GI and colon targeting

EUDRAGIT
Quick Starts
Enteric Coatings
Sustained-release Formulations
Protective Coatings
Melt Extrusion
Regulatory & Toxicology
Packaging & Delivery

Sustained-release Formulations

Sustained-release EUDRAGIT® formulations are employed for many oral dosage forms to e ingredients. Drug delivery can be controlled throughout the whole gastro-intestinal tract for i compliance. Different polymer combinations of EUDRAGIT® RL and RS grades allowing cu of alternatives to achieve the desired drug delivery performance.The EUDRAGIT® NE polyn plasticizer and is particularly suitable for granulation processes in the manufacture of matrix

There are two formulation options:

- EUDRAGIT® is employed as a coating material,usually for the coating of pellets or par compressed into tablets. These pellets or particles act as diffusion cells in the digestive per unit of time (multi-unitdosage forms).
- EUDRAGIT® serves as a matrix by which the active ingredient is embedded. The matri compression,granulation, or melt techniques.

Applications	EUDRAGIT® Grades	Availability	Functionality
Sustained release formulations	EUDRAGIT® RL 30 D EUDRAGIT® RL PO EUDRAGIT® RL 100	Aqueous dispersion 30% Powder Granules	Meth-/ acrylates copolyme trimethyl-ammonioethylme as a functional group
Sustained release formulations	EUDRAGIT® RS 30 D EUDRAGIT® RS PO EUDRAGIT® RS 100	Aqueous dispersion 30% Powder Granules	
Sustained release formulations, suitable for matrix structures and miscible with other EUDRAGIT® grades	EUDRAGIT® NE 30 D EUDRAGIT® NM 30 D EUDRAGIT® NE 40 D	Aqueous dispersion 30% Aqueous dispersion 40%	Neutral polymer of meth-/

Application benefits of EUDRAGIT® coatings with sustained drug release:

- Time-controlled release of activeingredient
- Therapeutically customized releaseprofiles
- Higher patient compliance dueto reduced number of doses tobe taken
- Cost-effective processing